

# Articles for Technicians

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## Dealing With Chemotherapy Extravasations: A New Technique

Doxorubicin, vincristine, and vinblastine are chemotherapeutic drugs commonly used in the treatment of cancer in pets. It takes technical skill to administer these drugs, because they are caustic sclerotics. If doxorubicin is extravasated into the perivascular tissues, the results may be devastating. The attending nurse and clinician must act vigorously to immediately remove every drop of the drug spilled into the tissues. Unfortunately, little has been written on how to effectively do that, but this paper describes an aggressive technique that can be used to combat such a spill. *J Am Anim Hosp Assoc* 2006;42:321-325.

Alice Villalobos, DVM

### Introduction

Certain chemotherapeutic drugs are caustic and cause a variable degree of sclerosis of perivascular tissues (i.e., localized tissue injury around the vein, resulting from a perivascular leak or spill). Doxorubicin is the most potent sclerotic chemotherapeutic agent commonly used in small animals.<sup>1-3</sup> Tissue injury can be extensive if the extravasation goes undetected and untreated. Even small amounts of doxorubicin can create severe, irreversible tissue damage. Actinomycin D is also a severely caustic agent. Vincristine, vinblastine, and mechlorethamine are moderately caustic.<sup>4</sup> Cisplatin, mitoxantrone, dacarbazine, 5-fluorouracil, mithramycin, etoposide, streptozotocin, and bleomycin are considered mild vesicants and are, therefore, mildly caustic.<sup>4</sup> It is important to classify drugs according to their potential for causing perivascular sclerosis. It is helpful to use chemotherapy treatment forms that have a warning box for the doctor to circle or check when the drug is ordered, so the nursing staff is alerted that localized tissue injury will result if there is a leak or spill.

Most perivascular leaks are noticed right away. A bleb or swelling appears immediately adjacent to the venipuncture site. Some animals experience immediate discomfort and will squirm, cry out, or struggle. When a leak is suspected, the nursing staff should feel free to point out (in a forceful manner) the problem to the attending doctor. For leaks that initially go undetected, the client may notice a problem within hours or up to 10 days following administration of the chemotherapy. The pet starts licking the venipuncture site, and then pain, swelling, inflammation, desquamation, and/or limping may occur [Figure 1].<sup>5</sup>

From the Animal Oncology Consultation Service, 20051 Ventura Boulevard, Woodland Hills, California 91364; 20805 Hawthorne Boulevard, Torrance, California 90503; and the Pawspice Care Clinic, 11057 East Roscrans Avenue, Norwalk, California 90650.



**Figure 1**—Site of extravasation on the left rear leg of a 9-year-old, castrated male Siberian husky 10 days after doxorubicin administration. Note the severe inflammation, desquamation, ulceration, and swelling over the saphenous vein area. The lesion continued to worsen over a 2-month period. (Reprinted with permission from Villalobos AE. *Canine and Feline Geriatric Oncology, Honoring the Human-Animal Bond*. Ames, IA: Blackwell, in press.)

### Sedation for Caustic Chemotherapy

Animals that resist manual restraint during the administration of any caustic chemotherapeutic agent require sedation. Sedation is recommended to help avoid accidental extravasation, and sedation is always recommended by the author when doxorubicin is to be administered. With doxorubicin, the client must be educated as to the potential for very serious and severe tissue damage that could ultimately require amputation in the event of extravasation. The attending staff must be vigilant in deciding which animals need sedation and which do not.

When sedating chemotherapy patients for doxorubicin administration, avoid acepromazine, other phenothiazines, and drugs that cause arrhythmias or vasodilation. A combination of low-dose medetomidine, butorphanol, and atropine can be given intravenously (IV) [see Table]. After chemotherapy administration is completed, the medetomidine is reversed with atipamezole. This combination of drugs is well tolerated by most relatively healthy cancer patients. Tiletamine/zolazepam<sup>a</sup> (2 to 4 mg/kg intramuscularly [IM]) is preferred by some clinicians for immobilization of healthy, fractious dogs. Animals with heart disease, advanced age, or cachexia are at higher risk when sedated. In these animals, a combination of fentanyl<sup>b</sup> (5 to 10 µg/kg IV), which is a short-acting opioid, and midazolam<sup>c</sup> (0.1 to 0.2 mg/kg IV), a short-acting benzodiazepine, can be used to avoid bradycardia. A combination of butorphanol<sup>d</sup> (0.2 to 0.4 mg/kg IV, IM) and diazepam<sup>e</sup> (0.2 to 0.5 mg/kg IV, IM) is also safe and effective. These latter drugs can be used in animals that are old and frail or have weight loss, chronic renal failure, heart disease, and/or diabetes. Many clinicians

prefer to administer inhalation anesthesia with sevoflurane or isoflurane via a mask or closed chamber to geriatric cats with cancer. The objective of sedation is to immobilize the animal to allow the safe administration of caustic, sclerotic chemotherapeutic drugs.

### Client Relations

Inexperienced clinicians and nursing staff may not fully understand the consequences of a doxorubicin extravasation, because the ramifications are hard to imagine unless they have been witnessed. When an extravasation occurs, it is important not to understate the problem to the client. It is probably best to describe the worst-case scenario to clients from the start. The client must be carefully counseled that the site will most likely slough and worsen initially. Educate the client that tissue damage happens despite the best wound management and nursing care.

It is also essential to apologize for the accident and empathize with the client's concerns. Insurance companies are teaching and encouraging physicians to apologize and empathize with their human patients whenever complications are encountered. Fewer complaints and less bitterness occur when the doctor has offered an apology for the patient's aggravation and discomfort from complications. Veterinary facilities often offer to absorb most of the cost of supportive care when dealing with extravasations. Having the client sign an informed consent form prior to chemotherapy administration may allow for other arrangements. This form may specifically outline the risk of extravasation and the potential costs of supportive care.

A full explanation of the consequences of extravasation helps the client understand why it is imperative to sedate a nervous and fractious animal prior to administering a caustic chemotherapeutic drug, especially doxorubicin.

### Clinical Course

The extravasation site may not look serious at first—even after the first 3 to 10 days. Vincristine sloughs usually become evident within the first 1 to 7 days. The damaged tissue forms necrotic crusts that feel like leather. When the dead tissue sloughs, it may leave a cutaneous ulcer that eventually heals over a 6-week period. Doxorubicin sloughs may appear after 7 to 10 days. The affected area appears inflamed for the initial 1 to 3 weeks, and then the lesion worsens over 2 to 3 months. The lesion may deepen and expose muscle, tendons, and bone. The eschar (i.e., a dark, demarcated, full-thickness necrotic area) enlarges and may become secondarily infected with organisms that are difficult to treat.

The wound must be treated daily with saline rinses and hydrophilic dressings to help remove caustic residues from the tissues. Bandages are changed daily to minimize bacterial infections and to monitor healing.<sup>4</sup> The animal should be given drugs that adequately control pain. Surgical debridement may be needed to remove necrotic tissue from the site. A grading system (1 through 5) for adverse events following chemotherapy describes a grade 4 soft-tissue

Table

Dosages of Sedatives Used to Facilitate Administration of Caustic Chemotherapeutic Agents\*

Body Weight		Medetomidine		Butorphanol	Atropine
(lb)	(kg)	Low Dose (mL)	High Dose (mL)	(mL)	(mL)
1	0.45	0.005	0.009	0.005	0.25
5	2.27	0.023	0.046	0.025	0.25
10	4.54	0.045	0.091	0.05	0.25
15	6.8	0.068	0.137	0.075	0.25
20	9.1	0.091	0.182	0.075	0.25
25	11.3	0.114	0.228	0.075	0.5
30	13.6	1.136	0.273	0.075	0.5
35	15.9	0.159	0.319	0.075	0.5
40	18.1	0.182	0.364	0.075	0.5
45	20.4	0.205	0.410	0.075	0.5
50	22.7	0.227	0.455	0.075	0.5
55	24.9	0.250	0.501	0.075	1
60	27.2	0.273	0.546	0.075	1
65	24.9	0.295	0.592	0.075	1
70	31.8	0.318	0.637	0.075	1
75	34.0	0.341	0.683	0.075	1
80	36.3	0.355	0.710	0.075	1
85	38.6	0.386	0.774	0.075	1
90	40.8	0.409	0.819	0.075	1
95	43.1	0.432	0.865	0.075	1
100	45.4	0.455	0.910	0.075	1
105	47.7	0.477	0.956	0.075	1
110	50.0	0.500	1.001	0.075	1
115	52.3	0.523	1.047	0.075	1
120	54.5	0.545	1.092	0.075	1
125	56.8	0.568	1.138	0.075	1

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toxicity as disabling, requiring reconstruction and grafting, or a lesion that is life-threatening.<sup>5</sup> Decision-making regarding amputation of an affected leg is difficult. The risk to benefit ratio and prognosis for the overall survival of the animal must be taken into account when considering amputation.

### Preventing Extravasations

The discomfort and cost associated with extravasations are major motivations for preventing them. The room where chemotherapy is administered should be quiet and free of

distractions. Technicians and their assistants should be focused and unhurried throughout the procedure. A clean venipuncture is essential when placing the IV catheter. Constantly monitor the injection site visually, with careful attention to drug flow from start to finish. Ensure that the catheter or butterfly needle is still in the vein during the entire administration of every drop of the drug.

Some oncologists propose the use of an indwelling catheter and dilution of the doxorubicin into a small bag of saline, which is infused over 30 to 45 minutes. This technique

may yield larger extravasations, because a larger volume of fluid and drug may extravasate before being noticed. Other oncologists prefer to administer the doxorubicin through a well-placed, indwelling IV catheter with simultaneous, rapid infusion of saline over 15 to 20 minutes. The author prefers to administer doxorubicin directly into the vein via a small butterfly catheter ( $\leq 23$  gauge) under direct supervision, until every drop of the drug is given.

The total calculated dose of doxorubicin is diluted with sterile saline in a 12-mL syringe, to a total of 10 mL for the average cat. The dose for dogs is diluted with sterile saline or water to approximately 0.5 mL/kg, using a 35-mL syringe for small dogs and a 60-mL syringe for large dogs. The butterfly catheter is flushed with saline, and the diluted doxorubicin is carefully administered while frequently pulling back on the syringe just enough to see that blood is aspirated into the tubing. This aspiration verifies the catheter is well positioned and not resting against the wall of the vein. Doxorubicin is administered to cats slowly over 5 to 7 minutes, and it is administered to dogs at a slow, steady infusion rate over 15 to 20 minutes.

Another excellent option is to use a small-gauge butterfly catheter with 12-inch tubing attached to a three-way stopcock.<sup>6</sup> A 12-mL Luer-lock syringe containing 0.9% saline solution for flushing is attached to one port of the three-way stopcock, and the chemotherapy drug is attached to the other port. Flushing before and after drug administration is easily performed without switching from one syringe to another [Figure 2]. The chemotherapy nurse monitors flow of the drug and verifies the position of the catheter in the vein by the continual aspiration of small amounts of blood during the entire drug administration [Figure 3].

### Initial Treatment of Extravasations

If an extravasation is detected, act immediately to rectify the problem. Do not remove the catheter, but rather aspirate it and remove the offending drug before withdrawing the catheter.<sup>1-3</sup> Removal of 5 to 6 mL of blood from a cat and 10 mL from a dog should adequately evacuate the catheter and tubing. Insert a 27-gauge needle into the bleb created by the spill and aspirate as much of the drug as possible to minimize the amount of drug left at the site. Some references recommend flushing saline through the catheter to dilute residual drug at the site.<sup>1-4</sup>

Application of ice packs or cold compresses is recommended for 6 to 10 hours after spillage of doxorubicin, actinomycin-D, and mechlorethamine.<sup>1-4</sup> Warm compresses are to be applied for the first 3 to 4 hours after vincristine, vinblastine, and etoposide extravasations.<sup>1-4</sup> These compresses are applied in an effort to minimize the vesicants' toxicity. Warm compresses may help to disperse the drug into the circulatory system, while cold compresses may localize the drug and reduce its toxicity. It is disheartening, however, to realize that no currently applied procedures adequately prevent the devastating tissue damage that arises from anthracycline (i.e., doxorubicin family) extravasations.



**Figure 2**—Using a small-gauge butterfly catheter with 12-inch tubing attached to a three-way stopcock may help prevent extravasations when administering chemotherapy. A 12-mL Luer-lock syringe filled with 0.9% saline solution (for flushing) is placed at one port, and the chemotherapy drug is attached to the other port. (Reprinted with permission from Villalobos AE. *Canine and Feline Geriatric Oncology, Honoring the Human-Animal Bond*. Ames, IA: Blackwell, in press.)



**Figure 3**—The chemotherapy nurse closely monitors the administration of chemotherapy. Continuous aspiration of small amounts of blood verifies that the catheter remains in the proper place in the vein during drug administration. (Reprinted with permission from Villalobos AE. *Canine and Feline Geriatric Oncology, Honoring the Human-Animal Bond*. Ames, IA: Blackwell, in press.)



### Modified Villalobos Snake Bite Slit Technique

Following experience with severe, unresponsive extravasations, a more aggressive technique of flushing the site was developed.<sup>7</sup> Using a technique similar to that applied to snake bites, every caustic drug spill is treated as an emergency. Initially, any residual drug is aspirated from the catheter and the subcutaneous bleb. Saline is then infiltrated into the site as described above. The site is aseptically prepared for surgical incision. Using a sterile, 18-gauge needle, 10 to 30 parallel, deep skin incisions or slits are made over the site, avoiding the vein.<sup>9</sup> The slits extend into the perivascular subcutaneous tissues in a staggered fashion [Figure 4]. The slits may extend beyond the margins of the extravasation and around the entire limb if necessary. Saline or a crystalloid solution is infused into the entire site and around the limb for 20 to 45 minutes.

While infusing copious (1 to 2 L, depending upon the size of the animal) amounts of fluids, the tissue is gently squeezed, and fluid is expressed from the site. This action may help to remove some of the offending drug. For larger spills, an 18-gauge needle can be inserted into the deeper

parts of the limb (e.g., into muscle, fat), so these tissues can also be flushed. This allows the vesicant drug to ooze out with the fluids. During this procedure, all involved staff should wear protective eye shields, gowns, and gloves.<sup>9</sup>

Following the flushing, the animal is discharged with a light wrap over the site, with instructions for the owner to apply cold compresses for the next 24 hours. The site is rechecked weekly for 3 weeks to monitor for tissue damage, infection, and healing of the skin incisions.

### Conclusion

Prevention of extravasation of caustic chemotherapeutic agents is preferred by far. By using extreme care with an infusion technique, the animal may be spared the pain and discomfort of a slough at a chemotherapy injection site. The modified Villalobos technique is one measure of minimizing problems following extravasations of sclerotic chemotherapeutic drugs.

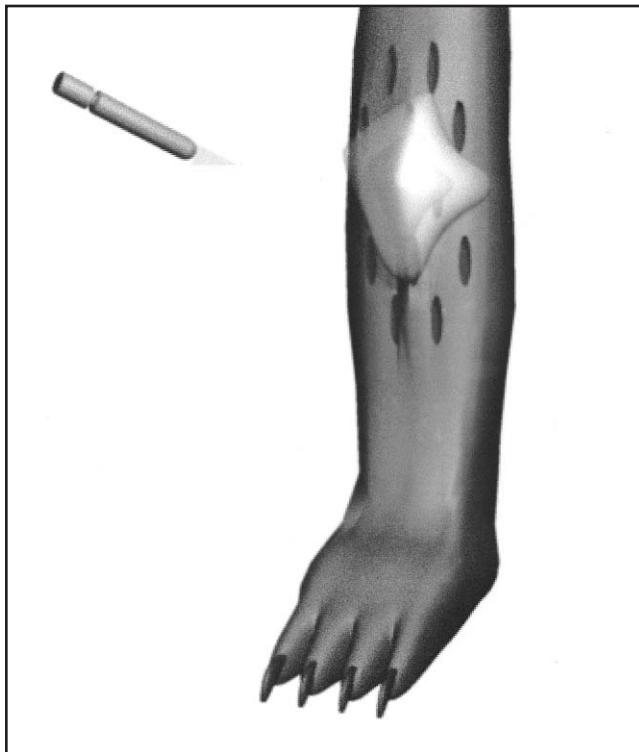
<sup>a</sup> Telazol; Fort Dodge, Fort Dodge, IA 50501

<sup>b</sup> Sublimase; Baxter Healthcare Corp., New Providence, NJ 07974

<sup>c</sup> Versed; Roche Pharmaceuticals, Nutley, NJ 07110-119

<sup>d</sup> Torbugesic; Fort Dodge, Fort Dodge, IA 50501

<sup>e</sup> Valium; Roche Pharmaceuticals, Nutley, NJ 07110-119



**Figure 4**—Illustration of the modified Villalobos snake bite slit technique that can be used for treating extravasations of caustic agents. A sterile, 18-gauge needle is used to make interrupted parallel skin incisions (slits) in a staggered fashion. The slits may extend beyond the extravasation site and around the entire limb as needed. Saline or crystalloid fluids are flushed into the subcutaneous tissues, and an effort is made to express the spilled vesicant drug and fluids out through the slits. (Reprinted with permission from Villalobos AE. *Canine and Feline Geriatric Oncology, Honoring the Human-Animal Bond*. Ames, IA: Blackwell, in press.)

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